IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: WALLACH=1D

In re Application of:	)	Conf. No.:
	)	
David WALLACH	)	Art Unit: 1646
	)	
Appln. No.: 10/036,434	)	Examiner: D. Jiang
	)	
Filed: January 7, 2002	)	Washington, D.C.
	)	
For: TUMOR NECROSIS FACTOR INHBITORY PROTEIN AND ITS PURIFICATION	)	June 20, 2007

SUPPLEMENTAL RESPONSE

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Amendments
401 Dulany Street
Alexandria, VA 22314

Sir:

The present communication supplements applicant's amendment and attached declaration of February 23, 2007. Attached hereto is a Second Declaration under 37 CFR §1.132 of Rik Derynck and ten exhibits.

On March 16, 2007, an advisory action was mailed relating to applicants amendment and declaration of February 23, 2007. On March 20, 2007, a Request for Continued Examination was filed, incorporating a petition for suspension of action for a period of three months pursuant to 37 CFR 1.103(c). Also submitted on March 20, 2007, was a Petition to

Revive Patent Application under 37 CFR §1.137(b). By communication of June 14, 2007, the petition to revive was granted. The present papers are being filed within the three month suspension period requested under 37 CFR 1.103(c) on March 20, 2007, and, accordingly, the present response and attached declaration must be fully considered in accordance with 37 CFR 1.111(a)(2)(ii).

The interview conducted between examiners Jiang and Spector, on the one hand, and the undersigned attorney and Dr. Rik Derynck, on the other hand, is hereby gratefully acknowledged. In this interview, the attached second declaration of Dr. Derynck was discussed. The undersigned and Dr. Derynck particularly pointed out that in Fig. 1 of Seckinger et al. (1988), the protein peak is very close to the activity peak and, therefore, there is really very little purification of the TNF inhibitory factor. In fact, a demonstration was made in which the two curves were pasted onto cardboard and the total amount of TNF inhibitory substance in the inhibitory peak (fractions 15 to 21) was compared to the total amount of TNF inhibitory protein under the rest of the curve. In a separate demonstration, the total amount of all protein that falls within the activity peak of fractions 15 to 21 was compared to the total amount of protein coming out in the remaining fractions. The cut-outs

demonstrated what can be seen in Exhibits G and H to the Derynck declaration, i.e., that at least twenty percent of the total protein elutes with the activity peak and that no more than about sixty percent of the TNF inhibitory protein falls under the activity peak. Thus, of the 20 mg of total protein loaded into the S-200 column, at least 4 mg of protein remains in the inhibitory fractions.

On the other hand, given that the Seckinger et al (1990) paper, which is of record in this case, shows that the same TNF inhibitory compound can be purified 81,000-fold as compared to the amount in the exact same material fed into the S-200 column in Seckinger et al. (1988), the amount of TNF inhibitory protein in the 20 mg of protein fed to the S-200 column was 1/81,000 of 20 mg or about 25 µg. Assuming a molecular weight for the protein of interest of about 30 kDa, this calculates to the presence of about 8 pmol of the protein of interest in the 20 mg sample of ammonium sulphate-precipitated protein that is loaded onto the S-200 column.

As no more than 60% is present in the active fractions, that means that the active fractions collected from the S-200 column could have contained no more than about 0.15 µg or 4.8 pmol of TNF inhibitory protein. All of this is explained in detail in the attached second declaration of Dr. Derynck, at pages 8-10.

It was further pointed out that the declaration further explains, with citation to literature references for factual support, that the minimum amount of protein reported as being necessary for N-terminal sequence analysis in 1988 was 5 pmol of purified protein, although more is usually required. The minimum amount is based on model studies in which highly purified and well characterized proteins were used under optimized conditions and not on an unknown protein being characterized for the first time. Thus, even if 100% of the S-200 active fractions could be loaded on an SDS-PAGE column, and even if 100% of the protein loaded appears in a single well defined band that can be identified as the TNF inhibitory band, there would still be insufficient protein (less than 5 pmol) for sequencing.

However, as further explained in the Derynck declaration, at pages 12-13, 50 µg of total protein is the maximum that can be loaded into a single column of SDS-PAGE. Thus, a 50 µg aliquot of the 4 mg of total protein in the active fractions from the S-200 column would contain only 1.25% of the total protein of interest - that is, only 0.06 pmol (1.8 ng) of protein. Not only could such a small amount not be sequenced, but the 1.8 ng of protein of interest is substantially beneath the minimum amount of protein per band

necessary for even the most sensitive silver staining, which requires a minimum of 0.1 µg of protein per band.

Finally, it was pointed out that SDS-PAGE is denaturing and, thus, it would be impossible to determine which of the myriad of bands that would appear on the gel is the band having TNF inhibitory activity. Again, all of this is explained in detail, with supporting documentation, in the second Derynck declaration attached hereto.

Thus, it was urged that the S-200 fraction of Seckinger et al. (1988), was much too impure to be sequenced and, even after being separated on an SDS-PAGE gel, the amount of protein was so small that it would not be stained or seen as a band and could not be sequenced on the equipment available at the time. Accordingly, one of ordinary skill in the art reading Seckinger et al. (1988) would not have been able to obtain the protein inhibitor of TNF-α in sufficient purity to allow determination of the N-terminal amino acid sequence, regardless of the discussion therein relating to SDS-PAGE.

The examiners at the interview agreed that this argument was persuasive and that, upon submission of the declaration, the present prior art rejection would be withdrawn. Examiner Spector also pointed out that she had studied the section of the MPEP relating to the patentability

of chemical compounds that differ from the prior art by degree of purity and that she agreed that the very substantial difference in purity here was sufficient to warrant patentability. Furthermore, Examiner Spector stated that, in view of the very crude stage of purity of Seckinger et al. (1988), she agreed that it would not have been obvious how to purify it to the stage of purity required for the present claims. She further noted that the present claims require that the protein be used for a therapeutic use and, therefore, the protein must be biologically active.

The examiners stated, however, that it would be necessary to evaluate other existing patents and/or pending applications as potential prior art or potential interfering subject matter with respect to the instant claims. Such further analysis is welcomed, but applicant doubts whether any relevant prior art not already cited during the prosecution of this, or any of its parent applications that have already issued as patents, exists. Applicant further doubts that there may be any pending patent applications claiming the same invention with an effective filing date as early as the 1988 effective filing date of the present application (even if one disregards the Israeli priority application date from which the present application claims benefit).

Accordingly, it is requested that the attached Second Declaration under 37 CFR 1.132 of Rik Derynck be entered and made of record in the present application and that, for the reasons presented therein, as well as presented at the interview, as well as presented herein, the present rejection of record be withdrawn and the present application passed to issue.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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